METAXALONE PRODUCTS, METHOD OF MANUFACTURE, AND METHOD OF USE

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation of U.S. application Ser. No. 11/364,468 filed Feb. 28, 2006, now U.S. Pat. No. 7,122,566, which is a continuation of U.S. application Ser. No. 11/349,534 filed Feb. 6, 2006, which claims the benefit of U.S. Provisional Application Ser. No. 60/726,861 filed Oct. 14, 2005, all of which are hereby incorporated by reference in their entirety.

BACKGROUND

This application relates to metaxalone products for therapeutic purposes, and in particular to improved methods of use of metaxalone.

Metaxalone, 5-[(3,5-dimethylphenoxy) methyl]-2-oxazolidinone, is used as a skeletal muscle relaxant. The mechanism of action of metaxalone in humans has not been established but may be due to general central nervous system depression.

Metaxalone was approved by the U.S. Food and Drug Administration (FDA) in 1962 as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions, such as muscles in spasm. Metaxalone is marketed in the United States under the brand name SKELAXIN®. The dosage forms currently approved for marketing are tablets containing 400 milligrams (mg) or 800 mg of metaxalone. The currently recommended dose for adults and children over 12 years of age is 800 mg, three to four times a day.

Food can affect gastric emptying, and may also alter the release of an active agent from a dosage form, the solubilization of the active agent, and the transport of the active agent across the intestinal wall. For lipophilic, water-insoluble active agents, fatty meals can increase gastric residence time thereby increasing the time available for solubilization and also may enhance the solubilization of the active agent by the lipids contained in the meal. According to U.S. Pat. No. 6,407,128, evaluation of the effect of food on the pharmacokinetics of metaxalone showed that food increased the rate and extent of absorption of a 400 mg oral dosage form in humans.

Studies directed to possible interactions of metaxalone with other active agents have been limited. There have been no detailed studies of the specific enzymes involved in metabolism of metaxalone or of the inhibitory or inducing effects of metaxalone on any Phase I or Phase II metabolic enzymes. In particular, there appear to be no published studies of the inhibitory and inducing effects of metaxalone on particular human cytochrome p450 isozymes or the possible metabolism of metaxalone by particular human cytochrome p450 isozymes.

Several major enzymes and pathways are involved in drug metabolism. Pathways of drug biotransformation are usually divided into two major groups of reactions: Phase I and Phase II metabolism.

Some typical examples of Phase I metabolism include oxidation, hydrolysis and reduction. Examples of Phase I enzymes involved in oxidation reactions are the cytochrome p450 monooxygenase system, the flavin-containing monooxygenase system, alcohol dehydrogenase and aldehyde dehydrogenase, monoamine oxidase, and peroxidases for co-oxidation. Examples of Phase I enzymes involved in reduction are NADPH-cytochrome p450 reductase and reduced (ferrous) cytochrome p450. Examples of Phase I hydrolysis enzymes are epoxide hydrolase, esterases and amidases.

Phase II metabolism involves conjugation reactions. Typical conjugation reactions are glucuronidation, sulfation, amino acid conjugation, acetylation, methylation, and mercapturic acid conjugation. Examples of Phase II metabolic enzymes are glutathione S-transferases (GSTs), mercapturic acid biosynthetic enzymes (transpeptidases, peptidases, and N-acetylases), UDP-glucoron(os)yltransferases, N-acetyltransferases, amino acid N-acyl transferases, and sulfotransferases.

One of the most important groups of Phase I enzymes are the cytochrome p450 monooxygenase system enzymes. The cytochrome p450 enzymes are a highly diverse superfamily of enzymes. NADPH is required as a coenzyme and oxygen is used as a substrate. Each enzyme is termed an isoform or isozyme since each derives from a different gene.

Many members of the cytochrome p450 family are known to metabolize active agents in humans. Active agent interactions associated with metabolism by cytochrome p450 isoforms generally result from enzyme inhibition or enzyme induction. Enzyme inhibition often involves competition between two active agents for the substrate binding site of the enzyme, although other mechanisms for inhibition exist. Enzyme induction occurs when an active agent activates an enzyme or stimulates the synthesis of more enzyme protein, enhancing the enzyme's metabolizing capacity.

Cytochrome p450 isozymes identified as important in active agent metabolism are CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Examples of cytochrome p450 enzymes known to be involved in active agent interactions are the CYP3A subfamily, which is involved in many clinically significant active agent interactions, including those involving nonsedating antihistamines and cisapride, and CYP2D6, which is responsible for the metabolism of many psychotherapeutic agents, such as thioridazine. CYP3A4 and CYP1A2 enzymes are involved in active agent interactions involving theophylline. CYP2C9, CYP1A2, and CYP2C19 are involved in active agent interactions involving warfarin. Phenytoin and fosphenytoin are metabolized by CYP1A2, CYP2C9, CYP2C19, and CYP3A4; mexiletine is metabolized by CYP2D6 and CYP1A2; and propafenone is metabolized by CYP2D6, CYP3A4, and CYP1A2.

Additionally, several cytochrome p450 isozymes are known to be genetically polymorphic, leading to altered substrate metabolizing ability in some individuals. Allelic variants of CYP2D6 are the best characterized, with many resulting in an enzyme with reduced, or no, catalytic activity. Gene duplication also occurs. As a result, four phenotypic subpopulations of metabolizers of CYP2D6 substrates exist: poor (PM), intermediate (IM), extensive (EM), and ultrarapid (UM). The genetic polymorphisms vary depending on the population in question. For example, Caucasian populations contain a large percentage of individuals who are poor metabolizers, due to a deficiency in CYP2D6—perhaps 5-10% of the population, while only 1-2% of Asians are PMs. CYP2C9, which catalyzes the metabolism of a number of commonly used active agents, including that of warfarin and phenytoin, is also polymorphic. The two most common CYP2C9 allelic variants have reduced activity (5-12%) compared to the wild-type enzyme. Genetic polymorphism also occurs in CYP2C19, for which at least 8 allelic variants have been identified that result in catalytically inactive protein. About 3% of Caucasians are poor